AMENDMENT TO THE CLAIMS

1. (Currently Amended) A method of biomarker discovery, said method comprising the steps of:

providing a complex analyte mixture sample, said sample comprising proteins and peptides, as a candidate biomarker source, said complex analyte mixture sample being depleted of ~~abundant~~ proteins that are less than 10% of the total number, and simultaneously represent at least 50% of the total mass, of proteins and peptides in said sample, said depleted proteins and peptides being denominated abundant proteins;

providing a control sample for said complex analyte mixture sample;

injecting a model animal with an aliquot of said abundant protein-depleted complex analyte mixture sample as an immunogen so as to generate, from individual hybridoma cell lines, a population of monoclonal antibodies directed against antigens in said complex analyte mixture sample;

screening said population of monoclonal antibodies directed against antigens in said complex analyte mixture sample against another aliquot of said complex analyte mixture sample;

screening said population of monoclonal antibodies directed against antigens in said complex analyte mixture sample against an aliquot of said control sample; and

selecting at least one monoclonal antibody that exhibits a statistically significant difference in binding to an antigen in said complex analyte mixture sample compared to an antigen in said control sample, whereby the antigen(s) selectively bound by said at least one selected monoclonal antibody are said biomarker(s).

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2. (Currently Amended) The method of claim 1, wherein, in said selecting step, said one or more monoclonal antibodies exhibits an increase in binding to an antigen in said complex analyte mixture sample compared to an antigen in said control sample.

3. (Withdrawn/Currently Amended) The method of claim 1, wherein, in said selecting step, said one or more monoclonal antibodies exhibits a decrease in binding to an antigen in said complex analyte mixture sample compared to an antigen in said control sample.

4. (Withdrawn/Currently Amended) The method of claim 1, wherein said complex analyte mixture sample is diluted before use as an immunogen.

5. (Currently Amended) The method of claim 1, wherein said complex analyte mixture sample is depleted of abundant proteins by fractionation before use as an immunogen.

6. (Currently Amended) The method of claim 1, wherein said complex analyte mixture sample is a clinical sample.

7. (Withdrawn/Currently Amended) The method of claim 6, wherein said complex analyte mixture sample is a human bodily fluid.

8. (Withdrawn/Currently Amended) The method of claim 7, wherein said complex analyte mixture sample is human blood.

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9. (Withdrawn/Currently Amended) The method of claim 8, wherein said complex analyte mixture sample is human plasma.

10. (Withdrawn/Currently Amended) The method of claim 8, wherein said complex analyte mixture sample is human serum.

11. (Withdrawn/Currently Amended) The method of claim 7, wherein said complex analyte mixture sample is human urine.

12. (Withdrawn/Currently Amended) The method of claim 7, wherein said complex analyte mixture sample is human cerebrospinal fluid.

13. (Cancelled)

14. (Withdrawn/Currently Amended) The method of claim ~~13~~1, wherein said complex analyte mixture sample comprises glycoconjugated proteins or peptides.

15. (Withdrawn/Currently Amended) The method of claim ~~13~~1, wherein said complex analyte mixture sample comprises a group of disease specific proteins.

16. (Cancelled)

17. (Currently Amended) The method of claim 1, wherein said complex analyte mixture sample is enriched in a ~~specific~~ class of analyte elements before use as an immunogen.

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18. (Currently Amended) The method of claim 6, wherein said complex analyte mixture sample is from an individual patient, wherein said control sample is from one or more healthy individuals and whereby said selecting step identifies a biomarker that distinguishes said patient from said healthy individuals.

19. (Withdrawn/Currently Amended) The method of claim 6, wherein said complex analyte mixture sample is from an asymptomatic individual having increased risk for the disease of interest, wherein said control sample is from one or more healthy individuals and whereby said selecting step identifies a biomarker that distinguishes said asymptomatic individual from said healthy individuals.

20. (Withdrawn/Currently Amended) The method of claim 6, wherein said complex analyte mixture sample is from an individual patient who has responded to a treatment, wherein said control sample is from an individual patient who has not responded to said treatment and whereby said selecting step identifies a biomarker that distinguishes an individual patient who will respond to said treatment from an individual patient who will not respond to said treatment.

21. (Original) The method of claim 1, further comprising the step of determining the identity of said biomarker(s).

22. (Previously Presented) The method of claim 1, further comprising the steps of determining the identity of a plurality of said biomarkers.

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23. (Currently Amended) A method of biomarker discovery, said method comprising the steps of:

providing a complex analyte mixture sample, said sample comprising proteins and peptides, as a candidate biomarker source, said complex analyte mixture sample being depleted of ~~abundant~~ proteins that are less than 10% of the total number, and simultaneously represent at least 50% of the total mass, of proteins and peptides in said sample, said depleted proteins and peptides being denominated abundant proteins;

providing a control sample for said complex analyte mixture sample;

injecting a model animal with an aliquot of said abundant protein-depleted complex analyte mixture sample as an immunogen so as to generate, from individual hybridoma cell lines, a population of monoclonal antibodies directed against antigens in said complex analyte mixture sample;

screening said population of monoclonal antibodies directed against antigens in said complex analyte mixture sample against another aliquot of said complex analyte mixture sample;

screening said population of monoclonal antibodies directed against antigens in said complex analyte mixture sample against an aliquot of said control sample;

selecting a plurality of monoclonal antibodies that each exhibits a statistically significant difference in binding to an antigen in said complex analyte mixture sample compared to an antigen in said control sample, whereby the antigens selectively bound by said plurality of selected monoclonal antibodies are a plurality of said biomarkers; and

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determining the identity of said plurality of biomarkers.

24. (Cancelled)

25. (Currently Amended) A method of generating a monoclonal antibody library related to a ~~specific~~ disease or condition, said method comprising the steps of:

providing a complex analyte mixture sample related to a ~~specific~~ disease or condition, said sample comprising proteins and peptides, as a candidate biomarker source, said complex analyte mixture sample being depleted of ~~abundant~~ proteins that are less than 10% of the total number, and simultaneously represent at least 50% of the total mass, of proteins and peptides in said sample, said depleted proteins and peptides being denominated abundant proteins;

providing a control sample for said complex analyte mixture sample;

injecting a model animal with an aliquot of said abundant protein-depleted complex analyte mixture sample as an immunogen so as to generate, from individual hybridoma cell lines, a population of monoclonal antibodies directed against antigens in said complex analyte mixture sample ;

screening said population of monoclonal antibodies directed against antigens in said complex analyte mixture sample against another aliquot of said complex analyte mixture sample;

screening said population of monoclonal antibodies directed against antigens in said complex analyte mixture sample against an aliquot of said control sample; and

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selecting a plurality of monoclonal antibodies that each exhibits a significant difference in binding to an antigen in said complex analyte mixture sample compared to an antigen in said control sample, whereby the plurality of monoclonal antibodies selected as exhibiting a significant difference in binding to an antigen in said complex analyte mixture sample compared to an antigen in said control sample is said monoclonal antibody library related to said ~~specific~~ disease or condition.

26. (Currently Amended) A method of biomarker discovery, said method comprising the steps of:

providing a complex analyte mixture sample, said sample comprising proteins and peptides, as a candidate biomarker source, wherein said complex analyte mixture sample is related to a biological process of interest;

providing a control sample for said complex analyte mixture sample;

depleting said complex analyte of one or more ~~abundant~~ proteins that are less than 10% of the total number, and simultaneously represent at least 50% of the total mass, of proteins and peptides in said sample, said depleted proteins and peptides being denominated abundant proteins;

injecting a model animal with an aliquot of said abundant protein-depleted complex analyte mixture sample as an immunogen so as to generate, from individual hybridoma cell-lines, a population of monoclonal antibodies directed against antigens in said complex analyte mixture sample;

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screening said population of monoclonal antibodies directed against antigens in said complex analyte mixture sample against another aliquot of said complex analyte mixture sample;

screening said population of monoclonal antibodies directed against antigens in said complex analyte mixture sample against an aliquot of said control sample;

selecting a plurality of monoclonal antibodies that each exhibits a statistically significant difference in binding to an antigen in said complex analyte mixture sample compared to an antigen in said control sample, whereby the antigens selectively bound by said plurality of selected monoclonal antibodies are a plurality of said candidate biomarkers;

determining the identity of said plurality of biomarkers; and

identifying individual biomarkers among said plurality of biomarkers that are associated with specific changes in said biological process of interest.

27. (Cancelled)

28. (Currently Amended) The method of claim 6, wherein said complex analyte mixture sample is from two or more individual patients.

29. (Currently Amended) A method of biomarker discovery, said method comprising the steps of:

providing a human bodily fluid sample, said sample comprising proteins and peptides, as a candidate biomarker source, said human bodily fluid sample being depleted of ~~abundant~~ proteins that ~~have a numeric complexity of~~are less than 5-10% of the total number,

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and simultaneously represent at least 50% of the total mass, of proteins ~~of~~ and peptides in said sample;

providing a control sample for said human bodily fluid sample;

injecting a model animal with an aliquot of said abundant protein-depleted human bodily fluid sample as an immunogen so as to generate, from individual hybridoma cell lines, a population of monoclonal antibodies directed against antigens in said human bodily fluid sample;

screening said population of monoclonal antibodies directed against antigens in said human bodily fluid sample against another aliquot of said human bodily fluid sample;

screening said population of monoclonal antibodies directed against antigens in said human bodily fluid sample against an aliquot of said control sample; and

selecting at least one monoclonal antibody that exhibits a statistically significant difference in binding to an antigen in said human bodily fluid sample compared to an antigen in said control sample, whereby the antigen(s) selectively bound by said at least one selected monoclonal antibody are said candidate biomarker(s).

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